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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEVADA

AMARIN PHARMA, INC. *et al.*,

Plaintiffs,

v.

WEST-WARD PHARMACEUTICALS CORP., *et al.*,

Defendants.

Case No.: 2:16-cv-02525-MMD-NJK

(Consolidated with 2:16-cv-02562-MMD-NJK and 2:16-cv-02658-MMD-NJK)

PLAINTIFFS' OPENING *MARKMAN* BRIEF

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LIST OF ABBREVIATIONS

• **ApoB**	apolipoprotein B
• **ATP III**	Third Report of the National Cholesterol Education Program, Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)
• **ethyl-EPA**	ethyl eicosapentaenoic acid
• **FDA**	U.S. Food and Drug Administration
• **g**	gram(s)
• **HDL-C**	high-density lipoprotein cholesterol
• **IDL**	intermediate-density lipoprotein(s)
• **LDL**	low-density lipoprotein(s)
• **LDL-C**	low-density lipoprotein cholesterol
• **mg/dl**	milligram(s) per deciliter
• **NCEP**	National Cholesterol Education Program
• **POSA**	person of ordinary skill in the art
• **PTO**	U.S. Patent and Trademark Office
• **TG**	triglyceride
• **TLC**	Therapeutic Lifestyle Changes
• **VLDL**	very-low-density lipoprotein(s)
• **VLDL-C**	very-low-density lipoprotein cholesterol

I. INTRODUCTION

This patent litigation arises from the filing by Defendants of applications with FDA to market generic copies of Amarin's Vascepa® product. Vascepa® is used to treat patients with very-high or severely elevated triglyceride levels (≥ 500 mg/dl), also known as severe hypertriglyceridemia, by reducing triglyceride ("TG") levels. Not only are patients with severe hypertriglyceridemia at risk of developing pancreatitis, a potentially life-threatening condition, but treatment of these patients is a particularly complex endeavor. Specifically, prior to the claimed inventions, there was no satisfactory method to lower TGs in patients with severely elevated TG levels without increasing LDL-C, cholesterol associated with LDL particles (otherwise known as "bad cholesterol"). Increased LDL-C levels in patients with severely elevated TG levels was undesirable because higher levels of LDL-C are associated with increased risk of atherosclerotic coronary heart disease.

The parties dispute the meaning of twenty claim terms. All of the claims of the patents-in-suit are methods of treatment claims—methods that cover treatment of a distinct patient population (here, those with severe hypertriglyceridemia), by administering purified ethyl eicosapentaenoic acid ("ethyl-EPA"), with the purpose of causing specific lipid effects. Plaintiffs' proposed constructions are based on this underlying principle and reflect how a skilled artisan would understand the terms in the context of the patent claims, specification, and prosecution history. Defendants, by contrast, offer constructions that are inconsistent with how a skilled artisan would understand the terms in light of the intrinsic evidence. As just one example, Defendants ignore that the claims plainly refer to "pharmaceutical composition" as the ethyl-EPA composition that goes *into* a dosage form. By proposing a construction that would apparently include both the composition containing the ethyl-EPA *and* the capsule which

encompasses the composition, Defendants contradict the language and teachings of the patents, in a bid to either unduly restrict the claims or render them vague.

In addition, Defendants assert that six terms related to changes in LDL-C levels are indefinite. Prior to the claimed invention, a person of ordinary skill in the art understood that increases in LDL-C were a significant clinical concern when treating patients with TG levels above 500 mg/dl. The asserted claims were allowed, in part, due to the recognition that there was a long-felt need for a medication to treat patients with severe hypertriglyceridemia without increasing LDL-C or other lipid parameters. Given this context, which is discussed extensively throughout the intrinsic evidence, a skilled artisan would have understood the scope of the terms, which relate to changes in LDL-C levels, with reasonable certainty. Defendants cannot meet their high burden of establishing by clear and convincing evidence that the claims containing the LDL-C terms are indefinite.[1]

Accordingly, for the reasons described in more detail below, the Court should adopt Plaintiffs' constructions of the disputed claim terms and find that the LDL-C terms are not indefinite.

II. BACKGROUND OF THE INVENTION

"Hypertriglyceridemia" refers to elevated levels of TGs in the blood. Elevated TG levels are associated with a number of diseases and disorders, including pancreatitis and cardiovascular disease. (Miller Decl. ¶¶ 32, 34–35.) Patients with hypertriglyceridemia are separated into different classes depending on the level of TGs in their blood: borderline high (150–199 mg/dl), high (200–499 mg/dl), and severe (≥ 500 mg/dl). (Miller Decl. ¶ 33.)

[1] The LDL-C terms (*infra* §§ V.F, V.G., and V.H.) appear in 41 asserted claims, across 12 out of the 14 asserted patents.

Patients are divided into these classes because each class is considered distinct with respect to treatment goals and approaches to treatment. (Miller Decl. ¶ 34.) Patients with borderline-high or high TGs are understood to be at risk of atherosclerosis, referred to colloquially as "hardening of the arteries." (Miller Decl. ¶ 36.) The primary treatment goal for patients with borderline-high or high TGs is the reduction of atherosclerotic risk by decreasing LDL-C levels, often using a class of drugs known as statins. (Miller Decl. ¶ 36.) For patients with severely elevated TG levels (≥ 500 mg/dl), by contrast, the primary treatment goal is to reduce the risk of pancreatitis, a serious and potentially life-threatening condition, by decreasing TG levels. (Miller Decl. ¶¶ 34–35.) While the risk of atherosclerosis remains a concern for these patients, the priority is to reduce TG levels below 500 mg/dl before addressing the risk of atherosclerosis. (Miller Decl. ¶ 35.) Severely elevated TG levels in patients in the fasting state were understood to be due to an inhibition in clearance of a TG-rich particle, very-low density lipoproteins ("VLDL"). (Miller Decl. ¶¶ 30, 32.) Because removal of VLDL is inhibited in patients with severely elevated TG levels, these patients typically have elevated VLDL blood levels. (Miller Decl. ¶ 30.)

In healthy individuals, VLDL particles are removed by a process in which the VLDL particles are converted to intermediate-density lipoprotein ("IDL") particles, which are ultimately converted to low-density lipoprotein ("LDL") particles. (Miller Decl. ¶¶ 25–26.) During this process, TGs are removed and used throughout the body. (Miller Decl. ¶ 26.) In addition, various apolipoproteins are attached to lipoproteins. (Miller Decl. ¶¶ 24–25.) One apolipoprotein of particular importance—ApoB—is used to measure the total number of lipoprotein particles (VLDL, IDL, and LDL) because one ApoB protein is present per lipoprotein. (Miller Decl. ¶ 25.)

Approved therapies for severe hypertriglyceridemia in 2009 were associated with a number of undesirable side effects. (Miller Decl. ¶¶ 37–38.) It was well-known and expected that LDL-C levels in patients with severely elevated TGs would increase in response to certain TG-lowering medications such as fibrates and Lovaza®. (Miller Decl. ¶ 37.) In addition, fibrates were known to have potentially fatal side-effects when combined with a statin. (Miller Decl. ¶ 37.) Increased LDL-C levels in patients with severely elevated TGs was undesirable because higher levels of LDL-C are associated with increased risk of atherosclerotic coronary heart disease. (Miller Decl. ¶¶ 28, 83, 86.) Clinicians often prescribed additional medication or increased doses of existing LDL-C lowering therapy to combat increased LDL-C levels when treating patients with severely elevated TG levels. (Miller Decl. ¶ 83.) Niacin was another drug approved to treat patients with severely-elevated TG levels, however it was associated with side effects such as flushing, gout, and worsening of diabetic conditions. (Miller Decl. ¶ 37.)

III. PATENTS-IN-SUIT

All but one of the patents-in-suit[2] are entitled "Methods of treating hypertriglyceridemia" and are continuations (or continuations of continuations) of a patent not asserted in this case, U.S. Patent No. 8,293,727. Because these patents are continuations, their specifications are essentially identical.[3] The only asserted patent that is not a member of this family, the '594

[2] These are U.S. Patent No. 8,293,728 ("the '728 Patent") (Ex. 4), U.S. Patent No. 8,318,715 ("the '715 Patent") (Ex. 5), U.S. Patent No. 8,357,677 ("the '677 Patent") (Ex. 6), U.S. Patent No. 8,367,652 ("the '652 Patent") (Ex. 7), U.S. Patent No. 8,377,920 ("the '920 Patent") (Ex. 8), U.S. Patent No. 8,399,446 ("the '446 Patent") (Ex. 9), U.S. Patent No. 8,415,335 ("the '335 Patent") (Ex. 10), U.S. Patent No. 8,426,399 ("the '399 Patent") (Ex. 11), U.S. Patent No. 8,431,560 ("the '560 Patent") (Ex. 12), U.S. Patent No. 8,440,650 ("the '650 Patent") (Ex. 13), U.S. Patent No. 8,518,929 ("the '929 Patent") (Ex. 14), U.S. Patent No. 8,524,698 ("the '698 Patent") (Ex. 15), U.S. Patent No. 8,546,372 ("the '372 Patent") (Ex. 16), and U.S. Patent No. 8,617,594 ("the '594 Patent") (Ex. 17).

[3] For convenience, Amarin will cite here to the '728 Patent specification and prosecution history, except where otherwise indicated, to refer to the common specification of all but the '594 Patent.

Patent, is entitled "Stable pharmaceutical composition and methods of using same" and is not related to the other patents-in-suit. Thus, the specification for the '594 Patent is different.

The patents-in-suit claim methods of treating subjects with TG levels of at least 500 mg/dl with purified ethyl-EPA. Typically, method of treatment claims recite a method performed by a clinician, or under the guidance of a clinician, and are related to improving the health of the subject being treated. Thus, they are generally understood to be directed to the clinician administering the treatment. The perspective and understanding of the person of ordinary skill in the art, here a clinician with specific expertise related to the claimed method, is particularly important in interpreting method of treatment claim terms. (Miller Decl. ¶¶ 14–18.)

The asserted method of treatment claims are directed to a clinician treating a patient with severely elevated TG levels by administering highly purified ethyl-EPA, wherein the clinician intends to cause specific lipid effects. Of particular importance are the claim limitations on the intended effects of the recited pharmaceutical composition on lipids, such as LDL-C and ApoB. Prior to the claimed invention, there was no satisfactory treatment available to physicians to lower TGs in patients with severely elevated TG levels without increasing LDL-C. (Miller Decl. ¶¶ 37–39.)

During prosecution of the asserted patents, the applicants submitted data from a 12-week clinical trial that demonstrated that 2 g and 4 g per day of highly purified ethyl-EPA (referred to as AMR101 in the clinical trial), when administered to patients with severely elevated TG levels, unexpectedly reduced TGs without increasing LDL-C levels. (Miller Decl. ¶ 44.) This invention "fill[ed] a clinically important unmet medical need in view of the increase in LDL-C levels often

found with currently approved omega-3 and fibrate drugs." (Ex. 18,[4] '727 Patent File History, Weintraub Declaration I ¶ 16 (AMRN03058277).) The clinical trial also demonstrated that 4 g per day of highly purified ethyl-EPA unexpectedly reduced ApoB. The reduction in ApoB is a favorable lipid effect because it "suggests that [AMR101] reduces the number of atherogenic lipoproteins." (Ex. 18, '727 Patent File History, Bays Declaration I ¶ 16 (AMRN03058236).) The applicants submitted extensive evidence through declarations of multiple experts describing both the unexpected nature of the claimed methods, as well as the long-felt need for a TG-lowering therapy in patients with severely elevated TG levels that did not increase LDL-C.[5] In fact, the unexpected results and long-felt need met by the claimed invention "[j]ustified the allowance of the instant claims in their full scope." (Ex. 19, '728 Patent File History, 9/6/12 Notice of Allowance at 3–6 (AMRN00212745–48).)

At a general and high level, the method of treatment claims can be broken down into four main claim elements: (1) the method of treatment preamble; (2) identification of the subject with severely elevated TG levels; (3) administration of highly purified ethyl-EPA to the subject; and (4) the intended lipid effects of ethyl-EPA administration on the subject.[6] For example, Claim 1 of the '728 Patent recites:

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[4] Exhibits 1–29 are attached to the declaration of Dr. Michael Miller, filed concurrently herewith. Exhibits 30–32 are attached to the declaration of Megan Keane, filed concurrently herewith.

[5] *See, e.g.*, Ex. 18, '727 Patent File History, 5/18/11 Bays Declaration ("Bays Declaration I"); Ex. 18, '727 Patent File History, 5/26/11 Weintraub Declaration ("Weintraub Declaration I"); Ex. 18, '727 Patent File History, 9/19/11 Weintraub Declaration ("Weintraub Declaration II"); Ex. 18, '727 Patent File History, 1/8/12 Bays Declaration ("Bays Declaration II"); Ex. 18, '727 Patent File History, 5/8/12 Bays Declaration ("Bays Declaration III"); Ex. 19, '728 Patent File History, 6/26/12 Bays Declaration ("Bays Declaration IV").

[6] This table is meant to be a general summary of the asserted claims that is representative of most, but not all, of the asserted claims. The table is not intended to limit the scope of any of the claims.

Claim 1 of the '728 Patent	Claim Element
A method of reducing triglycerides	(1) the method of treatment preamble
in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising:	(2) identification of the subject with severely elevated TG levels
administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks	(3) administration of highly purified ethyl-EPA to the subject
to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.	(4) the intended lipid effects of ethyl-EPA administration on the subject

IV. LEGAL STANDARD

A. Claim Construction

A court "look[s] to the words of the claims themselves . . . to define the scope of the patented invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*) (internal quotation mark and citation omitted). "[T]he specification is *always* highly relevant to the claim construction analysis" and serves as "the single best guide to the meaning of a disputed term." *Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1363 (Fed. Cir. 2016) (quoting *Phillips*, 415 F.3d at 1315). "[T]he interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." *Phillips*, 415 F.3d at 1316 (citation omitted). While it is improper to import limitations into the claims from the specification, it is necessary to read the claims in light of the specification. *See id.* at 1315–16, 1323. A court may also consider a patent's prosecution history, "the complete record of the proceedings before the PTO." *Id.* at 1317. "Any

explanation, elaboration, or qualification presented by the inventor during patent examination is relevant, for the role of claim construction is to 'capture the scope of the actual invention' that is disclosed, described, and patented." *Fenner Invs., Ltd. v. Cellco P'ship*, 778 F.3d 1320, 1323 (Fed. Cir. 2015) (quoting *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296, 1305 (Fed. Cir. 2011)).

Courts may also consider extrinsic evidence such as expert testimony, dictionaries, and the usage of a claim term in prior art. *See, e.g.*, *Bos. Scientific Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 986–87 (Fed. Cir. 2009). Expert testimony can be useful for a variety of purposes, including "to provide background on the technology at issue, to explain how an invention works, to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Phillips*, 415 F.3d at 1318.

B. Invalidity under 35 U.S.C. § 112 (Indefiniteness)

The definiteness requirement of 35 U.S.C. § 112, ¶ 2 is met where claims "inform those skilled in the art about the scope of the invention with reasonable certainty," but Courts recognize that "absolute precision is unattainable." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). To determine whether a claim has a reasonably certain meaning, a court must assess the claims, as a skilled artisan would have understood them, when viewed in light of the prosecution history, the specification, and the claims as a whole. *Id.* at 2128. Defendants bear the burden of proving indefiniteness by clear and convincing evidence. *Sonix Tech. Co. v. Publ'ns Int'l, Ltd.*, 844 F.3d 1370, 1377 (Fed. Cir. 2017).

V. THE DISPUTED CLAIM TERMS

A. "concurrent lipid-altering therapy" and "concomitant lipid-altering therapy"[7, 8]

Amarin's Proposal	Defendants' Proposal
a medication to alter lipid levels in a subject whereby the medication is administered concurrently/concomitantly with the administration of a pharmaceutical composition comprising ethyl eicosapentaenoate	any treatment that can cause an alteration in lipid levels whereby such treatment takes place concurrently/concomitantly with the administration of a pharmaceutical composition comprising ethyl eicosapentaenoate

Whether a dispute exists here turns on what Defendants mean by "any treatment that can cause an alteration in lipid levels." If "any treatment" refers to medication, which would be consistent with the plain and ordinary meaning of "treatment," then it appears that the parties do not have a dispute. If, however, Defendants are proposing that "treatment" be broadened to include lifestyle modifications, such as diet and exercise,[9] then Amarin disagrees with their proposed construction.

Amarin's proposed construction is the plain and ordinary meaning of the term "concomitant lipid altering therapy" from the point of view of a skilled artisan. Terms such as "concomitant lipid altering therapy," "concurrent lipid altering therapy," and "combination lipid

[7] The claims containing these terms are: '728 Patent, claims 1, 8, 19; '715 Patent, claims 1, 12, 13, 16, 17, 19; '335 Patent, claim 22; '399 Patent, claim 1.

[8] The parties agree that "concurrent lipid altering therapy" and "concomitant lipid altering therapy," as they appear in the disputed terms, are synonymous and should be given the same construction. Therefore, the terms are used interchangeably in this section.

[9] Defendants have cited to the National Cholesterol Education Program's guidance on Therapeutic Lifestyle Changes in Appendix C of the Joint Claim Construction Statement (ECF No. 83), suggesting that Defendants may argue that "any treatment" includes actions such as lifestyle counseling, diet improvement, and exercise. (Miller Decl. ¶ 52.) It appears Defendants intend to argue that they do not infringe the patent claims because, in copying Amarin's prescribing information, they instruct physicians to administer ethyl-EPA "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dl) hypertriglyceridemia."

altering therapy" are used in the field to refer to multiple *medications* that are given at the same time. (Miller Decl. § VII.A.) As Plaintiffs' expert Dr. Michael Miller explains, a clinician would not refer to one medication, which is administered in conjunction with lifestyle counseling, as a "concomitant lipid altering therapy."[10] (Miller Decl. ¶¶ 53–54, 58.)

The specification clearly establishes that "concomitant lipid altering therapy" refers to treatment using lipid-altering ***medications***. The '728 Patent's specification, for example, associates the phrase "lipid-altering therapy" with ***medications*** indicated for the treatment of a lipid disorder: "for example statin, fibrate, niacin and/or ezetimibe therapy." (Ex. 4, '728 Patent at 12:43–46; *see also* Miller Decl. ¶ 55.) Furthermore, the sole example of the '728 Patent describes a protocol in which potential study subjects are categorized according to whether they are on "lipid-altering therapy" prior to the start of the study. (Ex. 4, '728 Patent at 13:56–14:5; *see also* Miller Decl. ¶¶ 56–57.) In this passage, "lipid-altering therapy" indisputably refers to two different *medication* based therapies: "statin therapy (with or without ezetimibe)" (*id*. at 13:60–65) and "non-statin, lipid-altering medications" (*id*. at 13:66–14:5). The patent also discloses that ***all*** study subjects underwent a "diet and lifestyle stabilization period" where they received counseling regarding the National Cholesterol Education Program ("NCEP") Therapeutic Lifestyle Changes ("TLC") diet and instructions on how to follow this diet. (*Id.* at 14:6–49). This is the case even for subjects ***not*** on "lipid-altering therapy" as used in the patents-in-suit. The only reasonable implication is that diet and lifestyle stabilization and counseling are not "lipid-altering therapy." (*See also* Miller Decl. ¶¶ 56–57.) By contrast, under Defendants' proposed construction, all of the patients in the sole example in the patent would be

[10] Dr. Michael Miller is the Director of the Center for Preventive Cardiology at the University of Maryland Medical Center, and has treated patients with hypertriglyceridemia for over 26 years. (Miller Decl. § I.)

excluded from the claims in the '728 patent, contrary to the established cannons of claim construction. *See Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276–77 (Fed. Cir. 2008) ("We normally do not interpret claim terms in a way that excludes embodiments disclosed in the specification. . . . [W]here claims can reasonably to [sic] interpreted to include a specific embodiment, it is incorrect to construe the claims to exclude that embodiment, absent probative evidence on [sic] the contrary.").

Moreover, as discussed above, *supra* Sections II and III, a focus of the prosecution history was the unexpected results of the claimed methods to avoid a rise in LDL-C and to lower ApoB in patients receiving the claimed treatment. (*See also* Miller Decl. ¶ 63.) Clinical trial data submitted during prosecution establishes that all patients in the study (treatment group and placebo group) that formed the basis for these unexpected results received lifestyle counseling. (*See, e.g.*, Ex. 18, '727 Patent File History, Bays Declaration I at AMRN03058248–50; *see also* Miller Decl. ¶ 44.) Together with the patent specification, this evidence makes clear that a skilled artisan would understand that the results seen in the treatment group are based on a combination of ethyl-EPA and diet and lifestyle counseling. Defendants' proposed construction excludes these patients and is inconsistent with the intrinsic evidence.

In addition, the prosecution histories of the patents-in-suit refer to "concomitant lipid-altering therapy" as medications. When describing the prior art, the Examiner pointed to patients on concomitant medications, and did not include those on non-drug therapy such as lifestyle changes, when discussing "concomitant lipid-altering therapy." For example, a prior art reference included a description of a study, including whether the subjects received "non-drug therapy" such as diet and exercise, or "concomitant drugs" such as antihyperlipidemic medications. (Miller Decl. ¶ 59.) In describing that prior art reference, the Examiner stated that

"[m]ost of the patients, except for 24 individuals, did not receive any ***concomitant lipid-altering therapy*** (see page 7, Table 4, under concomitant drugs)." (Ex. 19, '728 Patent File History, 4/4/12 Office Action at 4 (AMRN00212290) (emphasis added).) The 24 individuals referenced by the Examiner were the 24 individuals who received an antihyperlipidemic drug. (*Id.*; Ex. 19, '728 Patent File History, Katayama at 7 (Table 4) (AMRN00209162); *see also* Miller Decl. ¶ 59.) The Examiner thus understood the claim term "concomitant lipid-altering therapy" to refer to antihyperlipidemic *medication* and to not include "non-drug therapy" such as diet and exercise. A person of ordinary skill in the art reading the file history would reach the same conclusion. (Miller Decl. ¶ 59.)

Table 4 Patient's Background

Item	Classification	Cases
	* * * * *	
Non-drug therapy	No	128
	Yes	52
	Dietary	22
	Exercise	1
	Combination	29
History	No	116
	Yes	57
	Hypertension	8
	Ischemic heart disease	5
	Diabetes	4
	Others	41
	Unknown	7
Complication	No	55
	Yes	125
	Hypertension	74
	Ischemic heart disease	26
	Diabetes	23
	Others	47
Concomitant drugs	No	51
	Yes	129
	Ca blockers	51
	Antihyperlipidemic drugs	24
	ACE blockers	24
	Circulatory drugs	19
	Others	149

Ex. 19, '728 Patent File History, Katayama at 7 (Table 4) (AMRN00209162) (highlighting added).

The prescribing information for various lipid-altering medications is also instructive. These medications are indicated as an adjunct therapy to diet, demonstrating that the initial step taken by a clinician for a patient with severely elevated TG levels is lifestyle counseling, and that all patients being treated for lipid abnormalities will be counseled on lifestyle modifications before treatment is administered. (Miller Decl. ¶¶ 61–62.) Further, each label contains a section that reviews concomitant lipid therapy. (Miller Decl. ¶¶ 61–62.) These sections exclusively discuss other medications and not lifestyle counseling, again demonstrating that "concomitant lipid altering therapy" and "concurrent lipid altering therapy" refer to medications and not diet and exercise. (Miller Decl. ¶¶ 61–62.)

Finally, when combination lipid-altering therapy is discussed in the relevant medical literature, it refers to administration of two or more medications. (*See, e.g.*, Ex. 24, Jacobson at 374 (AMRN03130428) (discussing the "complementary metabolic effects of statins, bile acid resins (BAR, sequestrants), niacin (*ie*, nicotinic acid), and fibrates" as a "[r]ationale for Combination Lipid-Altering Therapy"); *see also* (Miller Decl. ¶ 64).)

Because Amarin's construction of "concurrent lipid altering therapy" and "concomitant lipid altering therapy" is consistent with the plain and ordinary meaning in the art and is supported by the intrinsic evidence, Amarin's construction should be adopted.

B. "[orally] administering/administered" [11]

Amarin's Proposal	Defendants' Proposal
No Construction Necessary / Plain and Ordinary Meaning	delivering/delivered into the body [or mouth]

The terms "[orally] administering" and "[orally] administered" are commonly used in method of treatment claims. Moreover, a person of ordinary skill would understand the ordinary and customary meaning of "[orally] administering/administered" such that a construction is not necessary. The main dispute between the parties appears to be whether the terms "administering" and "administered" in the asserted patents encompass treatment or prescription by a clinician, as well as delivery into the body under the direction of a clinician, or are limited to literal delivery into the patient's body. Defendants narrow "administering" and "administered" to delivery of the claimed composition into the patient's body or mouth, departing from the plain meaning of the terms as they would be understood by a skilled artisan.

A claim term is given its "ordinary meaning as understood by persons skilled in the art in question at the time of the invention. The plain meaning of claim language ordinarily controls unless the patentee acts as his own lexicographer and provides a special definition for a particular claim term or the patentee disavows the ordinary scope of a claim term either in the specification or during prosecution." *InterDigital Commc'ns, LLC v. ITC,* 690 F.3d 1318, 1324

[11] The claims containing these terms are: '728 Patent, claims 1, 2, 5–9, 12–14, 19; '715 Patent, claims 1, 2, 4–10, 13, 14, 17; '677 Patent, claims 1, 2, 6–9; '652 Patent, claims 1, 2, 6–11, 15–18; '920 Patent, claims 1, 2, 6–10; '446 Patent, claims 1, 4–7; '335 Patent, claims 1–3, 6–9, 14, 15, 18–23, 26–29; '399 Patent, claims 1, 2, 6–9; '560 Patent, claims 1, 4, 5, 6, 11, 14–17; '650 Patent, claims 1, 4–8, 11–14; '929 Patent, claim 1; '698 Patent, claims 1, 4, 5; '372 Patent, claims 1, 4–6, 10, 13–15, 17, 20–22; '594 Patent, claims 1, 4–6, 10, 13–15, 17, 20–22. The term "orally" does not appear with "administering" in the following independent claims: '335 Patent , claims 1, 14, 22; '728 Patent, claim 8. The rest of the recited claims include "orally administering" or "administering orally."

(Fed. Cir. 2012) (citations omitted). As the specification and prosecution history here does not disclaim any claim scope or otherwise define the terms, Plaintiffs are entitled to the full scope of the claim language. (*See* Miller Decl. ¶¶ 67–69.)

The term "administering" appears in all independent claims. The term "orally" appears in conjunction with some, but not all, of the "administering" terms in the independent claims.[12]

Claim 1 of the '728 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising: ***administering*** orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

The claims specify that the act of "administering" the claimed pharmaceutical composition is "to" the recited subject or patient population. The claims do not restrict the route of administration or limit the actor to a specific individual (i.e., the patient or the clinician). Thus, these method of treatment claims include actions taken by a clinician to administer the claimed pharmaceutical composition "to" the subject in order to treat his condition.

[12] The adverb "orally" clarifies that the route of administration is oral. The specification conveys that the composition of the invention may be in a form that can be ingested orally, but does not limit the term "administering orally" to exclude prescribing or instruction by a clinician to take the claimed composition orally. *See* Ex. 4, '728 Patent at 12:49–53 (describing "orally deliverable" and "oral administration" as "any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed").

Other courts have agreed that terms such as "administering" and "administered" in claims directed to medical treatment should not be so limited. For instance, in *Erfindergemeinschaft Uropep GbR v. Eli Lilly & Company*, the court explained:

> A person of ordinary skill would contemplate that the person 'administering' the drug is involved in the actual treatment of the patient (i.e., forming of a diagnosis for a health issue, devising a course of action to ameliorate that issue, or causing that course of action to be followed). . . . [I]t is clear that a physician who directs a patient to take a drug in pill form can be said to be 'administering' the drug to the patient even if the physician does not actually place the pills in the patient's mouth[.]

No. 2:15-CV-1202-WCB, 2016 WL 7042234, at *4 (E.D. Tex. Aug. 11, 2016). Indeed, the plain meaning of "administering" and "administered" as used in the claims encompass treatment or prescription by a clinician, as well as delivery into the body under the direction of a clinician. For example, in *GlaxoSmithKline LLC v. Glenmark Pharmaceuticals, Inc.*, the court construed the term "administering" as "prescribing, dispensing, giving or taking (such that what is prescribed, dispensed, given or taken is actually taken into a patient's body)." No. 14-cv-877, 2016 WL 3186657, at *17 (D. Del. June 3, 2016), *aff'd in relevant part,* 2017 WL 658468, at *1–2 (D. Del. Feb. 17, 2017). The court clarified that "the claims encompass scenarios in which a physician directly places a drug into a patient's body, scenarios in which a physician prescribes a drug for a patient to take elsewhere, and alternatives in between." *GlaxoSmithKline*, 2017 WL 658468, at *2 n.3.[13]

Dictionary definitions of the verb "administer" also confirm that "administering" extends beyond mere delivery into the body. (Miller Decl. ¶ 70.) For example, a medical dictionary

[13] The courts in *Erfindergemeinschaft* and *GlaxoSmithKline* provided constructions for "administering" which comport with the proper plain and ordinary meaning of the term. Plaintiffs do not believe a construction defining the plain and ordinary meaning of the "administering" and "administered" term is necessary.

defines "administration" as "[t]he giving of a therapeutic agent" (Ex. 25, Taber's Cyclopedic Medical Dictionary at AMRN03130551), and the Merriam-Webster's Collegiate Dictionary defines "administer" as "to manage or supervise the execution, use, or conduct of," "to mete out," and "to give remedially." (Ex. 26 at AMRN03130545; *see also* Miller Decl. ¶ 70.)

Dr. Miller explains that a person of ordinary skill in the art would understand that "administering" a pharmaceutical composition in the context of the method of treatment claims includes treatment, instruction, or prescribing by a clinician. (Miller Decl. § VII.B.) And his opinions are further supported by prescribing information for pharmaceuticals, which assume that administration encompasses many different acts by a physician. (S*ee, e.g.*, Ex. 18, '727 Patent File History, Lovaza® prescribing information at AMRN03059151 (instructing clinicians to "[a]ssess triglyceride levels carefully before initiating therapy" and that "[p]atients should be advised to swallow LOVAZA capsules whole"); *see also* Miller Decl. ¶ 69.)

There is no basis in the claims, specification, or prosecution history for Defendants' attempt to substitute "delivering/delivered into the body" for "administering/administered" and narrow the scope of this term. Defendants' proposed construction ignores the plain and ordinary meaning of the terms, as well as the realities of medical practice where a clinician must prescribe a FDA-regulated pharmaceutical product to a patient, and a patient takes the prescribed pharmaceutical product under the direction of the clinician. Defendants narrow "administering" and "administered" to delivery of the claimed composition into the patient's body or mouth, that departs from the plain meaning of the terms as they would be understood by a person of ordinary skill in the art.

C. "pharmaceutical composition" [14]

Amarin's Proposal	Defendants' Proposal
a composition suitable for inclusion in a dosage form for administration to patients	drug dosage form for administration

The sole dispute between the parties appears to be whether the term "pharmaceutical composition" in the relevant patents[15] refers to the ethyl-EPA composition inside the claimed capsules, or also includes the capsule shell along with the capsule's contents. Plaintiffs' proposed construction accords the term "pharmaceutical composition" its plain meaning in the context of the relevant patents, *i.e.*, "a composition suitable for inclusion in a dosage form for administration to patients." In contrast, Defendants' proposed construction, "drug dosage form for administration," would apparently include both the ethyl-EPA composition *and* the capsule that encompasses the ethyl-EPA composition. As explained below, Defendants' construction, which includes the capsule, would render the claims nonsensical. *See AIA Eng'g Ltd. v. Magotteaux Int'l S/A*, 657 F.3d 1264, 1276 (Fed. Cir. 2011) ("We strive, where possible, to avoid nonsensical results in construing claim language."); *Bd. of Regents of the Univ. of Tex. Sys. v. BENQ Am. Corp.*, 533 F.3d 1362, 1370 (Fed. Cir. 2008) ("We decline to adopt a construction that would effect this nonsensical result.").

The claims plainly refer to a "pharmaceutical composition" as the ethyl-EPA composition that goes *into* a dosage form. For example, Claim 1 of the '728 Patent recites that a subject is

[14] The claims containing these terms are: '728 Patent, claims 1-3, 5-10, 12-14, 16, 18, 19; '715 Patent, claims 1, 13, 14, 17; '677 Patent, claims 1-3, 6-9; '652 Patent, claims 1-3, 6-12, 15-18; '920 Patent, claims 1-3, 6-10; '650 Patent, claims 1, 8; '399 Patent, claims 1-3, 6-9; '335 Patent, claims 1, 2, 6-9, 13, 14, 18-22, 26-29; '929 Patent, claims 1, 8; '698 Patent, claims 1, 4, 5, 7; '372 Patent, claims 1, 17.

[15] The term "pharmaceutical composition" does not appear in the claims of the '560 patent, '446 patent, or '594 patent.

administered "4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, [ethyl-EPA.]" A person of ordinary skill in the art reading the claim would understand the "4 g" to be referring to the ethyl-EPA composition that is intended to cause the desired lipid effects. Only the weight of the active composition (ethyl-EPA composition), not the surrounding capsule, is relevant to clinical practice; referring to the entire dosage form (ethyl-EPA composition and capsule) as being 96% ethyl-EPA would be nonsensical. The purity of ethyl-EPA ("at least about 96%") only reasonably applies to the ethyl-EPA composition that goes into the dosage form. This is also how "4 g" is used in Example in the patent, to refer to 4 g of the ethyl-EPA composition. (Ex. 4, '728 Patent at 13:24–14:33.)

The dependent claims of the '728 Patent confirm that the "pharmaceutical composition" cannot include the dosage form. Claims 2 and 3 of the '728 Patent (emphasis added), which depend upon Claim 1, recite:

> **2.** The method of claim 1, wherein the pharmaceutical composition is administered to the subject 1 to 4 times per day.
>
> **3.** The method of claim 2 wherein, the pharmaceutical composition ***is present in*** one or more capsules.

Dependent Claim 3 states that the "pharmaceutical composition ***is present in***" a capsule.[16] These claims differentiate the capsule from the pharmaceutical composition, and require the pharmaceutical composition be "present in" the claimed one or more capsules. There is no question that the "pharmaceutical composition" in Claim 3, and accordingly in Claims 1 and 2,

[16] *See also* Claim 3 of the '920 Patent; Claim 8 of the '929 Patent; Claims 8 and 24 of the '372 Patent; Claims 4, 16, and 24 of the '335 Patent; Claim 7 of the '698 Patent; Claim 3 of the '715 Patent; Claim 3 of the '677 Patent; Claims 3 and 12 of the '652 Patent; Claim 3 of the '399 Patent.

refers to the *ethyl-EPA composition* that goes into a capsule. Similarly, the specification unmistakably describes the "pharmaceutical composition" as "the composition that is present in a capsule shell." (Ex. 4, '728 Patent at 1:41–54). The pharmaceutical composition is distinguished from the "dosage form," which is described as "a gel or liquid capsule." (*Id.* at 12:6–10).

Moreover, Amarin's proposed construction of the term is consistent with extrinsic evidence discussing dosage forms and pharmaceutical compositions at the time of the invention in 2009. The U.S. Pharmacopeia, the organization responsible for setting quality standards for drug products, describes testing of omega-3 products based on the weight of the oil (the active ingredient), not the entire dosage form. (Ex. 31, 1 United States Pharmacopeia, The National Formulary 1136 (2011) at AMRN03130557 ("Weight NLT 10 Capsules in a tared weighing bottle, carefully open the Capsules, without loss of shell material, and transfer the combined Capsule contests to a 100-mL beaker."). In addition, the weight of a dosage form, i.e. capsule, could be significant—approximately 300 to 400 mg each. (Ex. 30, Uni-Caps, LLC, Fish Oil 1000 Product Details at AMRN03130502.) Therefore, administration of 4 g of a drug dosage form (which includes the weight of the dosage form), as Defendants appear to propose, would depart from what is described throughout the patent, including the example.

Contrary to the intrinsic and extrinsic evidence, Defendants attempt to re-write the claim term, rendering the relevant claims inconsistent with clinical practice.

D. "to effect [a] . . .," "effective to . . .," "exhibits [a] . . .," and "effects [a] . . ." [17, 18]

Amarin's Proposal	Defendants' Proposal
Claim limitation encompassing the intentional purpose for which the method must be performed. Plain and ordinary meaning applies.	Claim limitation and not merely a statement of intended result or effect Plain and ordinary meaning

The "to effect [a] . . .," "effective to . . .," "exhibits [a] . . .," and "effects [a] . . ." terms (collectively, the "effect" terms), recite essential lipid effects of the claimed methods of treatment, such as "a reduction in triglycerides without substantially increasing LDL-C."[19] Accordingly, these terms should be construed to require that the clinician performing the claimed method have the specific intent to confer the claimed lipid effects to the subject. Defendants agree that these terms are limitations and assert that it is "not merely a statement of intended result or effect," but have not further explained their position as to what the terms mean.

Claim 1 of the '728 Patent is:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by

[17] The claims containing these terms are: '728 Patent, claims 1, 5–8, 12–14, 19; '715 Patent, claims 1, 4–10, 13, 14, 17; '677 Patent, claims 1, 6–9; '652 Patent, claims 1, 6–10, 15–18; '920 Patent, claims 1, 6–10; '446 Patent, claims 1, 4–7; '335 Patent, claims 1, 2, 6–9, 13, 14, 18–22, 26–29; '399 Patent, claims 1, 6–9; '560 Patent, claims 1, 4–7, 11, 14–17; '650 Patent, claims 1, 4–8, 11–14; '929 Patent, claims 4–6; '698 Patent, claims 1, 4, 5; '372 Patent, claims 4–6, 13–15, 20–22; '594 Patent, claims 1, 4–6, 10, 13–15, 17, 20–22.

[18] Exhibit C to the Joint Claim Construction and Prehearing Statement (ECF No. 83) inadvertently included the term "without effecting a" with this set of terms. The "without effecting a" term is addressed below in Section V. H "without effecting a statistically significant increase in LDL-C."

[19] In addition, Claim 5 of the '728 Patent recites "to effect a reduction in fasting non-HDL-C and a reduction in fasting VLDL-C;" Claim 5 of the '929 Patent recites "effective to reduce apolipoprotein B," and claim 9 of the '335 Patent recites "exhibits a reduction in fasting total cholesterol."

> weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks ***to effect a reduction in triglycerides without substantially increasing LDL-C*** compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

The claims convey that a clinician is performing the method with the intent ***to*** cause the claimed results. When an "intended objective" of the claim is "the essence or fundamental characteristic of the claimed invention," that objective is "an essential limitation to the claims." *Vizio, Inc. v. ITC* , 605 F.3d 1330, 1340–41 (Fed. Cir. 2010); *see also Manning v. Paradis,* 296 F.3d 1098, 1102-04 (Fed. Cir. 2002) (finding that "method of treating a subject in cardiac arrest" and the "in an amount effective to deliver oxygen to the heart of said subject" defined the "intended purpose of the invention."); *Griffin v. Bertina*, 285 F.3d 1029, 1033–34 (Fed. Cir. 2002) ("The manipulative steps set forth in the [claim] have little meaning or utility unless they are placed within the context of the diagnosis of an increased risk of developing thrombosis, recited in the preamble and 'wherein' clauses.").

The prosecution history leaves no doubt that the "effect" claim language encompasses the intended purpose of the method—to confer specific lipid effects to the subject—and is the "essence of the invention." (Miller Decl. ¶ 77.) The "effect" language was added to pending claims to overcome a rejection by the Examiner that the previously drafted limitations were not entitled to patentable weight. During prosecution, the Examiner took the position that clauses in the claims that were pending at the time, such as "wherein . . . the subject exhibits . . . substantially no increase in LDL-C," were not entitled to patentable weight because they "simply express[] the intended result of a process step positively recited." (Ex. 18, '727 Patent File History, 3/2/12 Office Action at 9–10 (AMRN03059753–54).) In response, Amarin amended the claims to add the "effect" language and explained that such a limitation "is often used in

association with an element, ingredient, or step of a process to define a particular capability or ***purpose*** that is served by the recited element, ingredient or step." (Ex. 18, '727 Patent File History, 5/16/12 Request for Continued Examination at 9 (AMRN03059797) (emphasis added) (citation omitted).) Moreover, the applicants relied on and submitted to the PTO as part of the file history *AstraZeneca AB v. Dr. Reddy's Laboratories, Ltd.* (Ex. 18, '727 Patent File History at AMRN03059851–65), and stated that *AstraZeneca* explains that "the allegedly inherent properties of the '[so as to effect] clauses' provide the necessary purpose to the steps." No. 05-5553 (JAP), 2010 WL 11414548, at *10 (D.N.J. May 18, 2010) (citation omitted); *see also Griffin*, 285 F.3d at 1033–34. As the Court explained in *Jansen v. Rexall Sundown, Inc.*, the revision of these terms "must be recognized and appreciated, for otherwise the added phrases do not carry the meaning that the circumstances of their addition suggest that they carry." 342 F.3d 1329, 1334 (Fed. Cir. 2003). Indeed, Defendants agree that the "effect" limitations are entitled to patentable weight. Thus the only reasonable approach is to give the limitations the meaning they were intended—to encompass the specific intent of the claimed methods.

Moreover, many of the "effect" limitations cover the unexpected results and the long-felt need met by the invention, both of which are discussed extensively in the prosecution history, and ultimately led to the allowance of the patent claims. (Ex. 18, '727 Patent File History, 9/6/12 Notice of Allowance at 6–9 (AMRN03059936–39); Ex. 19, '728 Patent File History, 9/6/12 Notice of Allowance at 3–6 (AMRN00212745–48).) And when the clause "states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005) (per curiam), *cert. denied*, 546 U.S. 1131 (2006). Dr. Miller explains that the claim language is consistent with the fact that when a clinician prescribes a drug, the physician does so with a prescribing

intent; in other words, to bring about certain effects. (Miller Decl. ¶ 76.) Therefore, a skilled artisan would understand the "effect" limitations to convey the intended benefit and purpose of the claims. (Miller Decl. ¶¶ 75–76.) Prior to the claimed methods, there was no satisfactory method that clinicians could use to lower TGs in patients with severely elevated TG levels without increasing LDL-C. (Miller Decl. ¶ 37.) Thus, based in the intrinsic record a skilled artisan would have understood the claims to cover the distinguishing feature of the claimed methods—to intentionally decrease TGs in patients with severely elevated TG levels without increasing LDL-C and/or also reducing ApoB—as well as the other claimed lipid effects. (Miller Decl. ¶ 77.)

E. "compared [to] . . ." [20]

Amarin's Proposal	Defendants' Proposal
No Construction Necessary / Plain and Ordinary Meaning	Claim limitation and not merely a statement of intended result or effect Plain and ordinary meaning

Many of the "effect" terms are followed by "compared [to]", which further describes the intended lipid effect on the subject as compared to baseline lipid levels, a second subject, a second patient population, or placebo control (depending on the claim). As such, the "compared [to]" terms are part and parcel of the larger "effect" claim limitation, as it further defines the intended lipid effect on the subject.

[20] The claims containing these terms are: '728 Patent, claims 1, 5–8, 12, 14, 19; '715 Patent, claims 1, 4–10, 17; '677 Patent, claims 1, 6–9; '652 Patent, claims 1, 6–10, 15–18; '920 Patent, claims 1, 6–10; '446 Patent, claims 1, 4–7; '399 Patent, claims 1, 6–9; '335 Patent, claims 1, 2, 6–14, 18–22, 26–29; '560 Patent, claims 11, 14–17; '650 Patent claims 8, 11–14; '698 Patent, claims 1, 4, 5.

Claim 1 of the '728 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks ***to effect*** a reduction in triglycerides without substantially increasing LDL-C ***compared to a second subject*** having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

A person of ordinary skill in the art would have readily understood the plain and ordinary meaning of these "compared [to]" terms, such that a construction is not necessary. *See Allergan, Inc. v. Sandoz, Inc.*, No. 6:11-CV-441, 2013 WL 1314188, at *6 (E.D. Tex. Mar. 28, 2013) (construing "as compared to . . . [a/the] second composition" as having its plain and ordinary meaning). Indeed, Defendants agree with this position and, similar to Plaintiffs, have proposed that the "compared [to]" terms be given their plain and ordinary meaning.

Both the specification and prosecution history of the patents-in-suit provide clear context of the claimed comparison. The example in the specification describes a study where the claimed purified ethyl-EPA composition was compared against a placebo. (Ex. 4, '728 Patent at 13:26–16:50.) The study was designed to observe how the claimed pharmaceutical composition affected lipid parameters such as TG, LDL-C, total cholesterol, and others, against both baseline lipid levels and the placebo group. *Id.*

Clinicians rely on clinical trials to provide information concerning the effects of the drugs that they use to treat patients. This type of evidence-based medicine is routine in clinical practice. (Miller Decl. ¶ 98.) Particularly in the context of the asserted method of treatment claims, a person of ordinary skill in the art would have understood "compared [to]" as further

defining the lipid effects produced by the claimed method, as evidenced by the results of a clinical trial. Thus, when reciting a comparison to baseline lipid levels, second subject, a second patient population, or placebo control, a skilled artisan would have understood that the claims refer to an intended lipid effect (*e.g.*, decreasing TGs without raising LDL-C), and that effect would be compared to, for example, the expectation if the subject did not receive purified ethyl-EPA, as described in the specification, prosecution history, and available clinical trial results.

F. "without substantially increasing LDL-C," "substantially no increase or a reduction in fasting LDL-C," "substantially no increase in LDL-C" [21]

Amarin's Proposal	Defendants' Proposal
without a clinically meaningful increase in LDL-C	Indefinite under 35 U.S.C. § 112

1. The Correct Construction Is "without a clinically meaningful increase in LDL-C"

When read in the context of the intrinsic evidence, it is clear that "without substantially increasing LDL-C," "substantially no increase in LDL-C," and "substantially no increase or a reduction in fasting LDL-C" each refer to the absence of a clinically meaningful increase in LDL-C. A person of ordinary skill in the art would understand that a "clinically meaningful increase in LDL-C" is an increase which would require clinical judgment concerning the subject's treatment regimen; for example, by adding additional lipid altering therapy or increasing the dose of existing therapy. Indeed, terms such as "substantially" and its various iterations are commonly used in patent claims and consistently understood in ascertaining the

[21] The claims containing these terms are: '728 Patent, claims 1, 8, 19; '677 Patent, claims 1, 6, 7; '652 Patent, claims 1, 6, 7, 10, 15, 16; '446 Patent, claims 1, 4, 5; '399 Patent, claims 1, 6, 7; '335 Patent, claims 2, 6; '715 Patent, claim 4.

scope of claims. *See, e.g.*, *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012).

During prosecution, experts described increases in LDL-C as substantial when discussing TG-lowering medications prior to the claimed invention, such as Lovaza® and fibrates. (Miller Decl. ¶¶ 83–85.) For example, Dr. Bays explained how, prior to the claimed invention, medications to lower TG levels often "increase[d] LDL-C levels, and sometimes ***substantially*** so especially in patients with very high TG levels." (Ex. 19, '728 Patent File History, Bays Declaration IV ¶ 40 (AMRN00212357) (emphasis added).) The substantial rise in LDL-C levels "present[ed] treatment challenges because lowering LDL-C is the primary lipid treatment target to reduce atherosclerotic coronary heart disease (CHD) risk." (Ex. 19,'728 Patent File History, Bays Declaration IV ¶ 40 (AMRN00212357).) Purified ethyl-EPA's ability to decrease TG levels without substantially increasing LDL-C (unlike previous TG-lowering therapies) was of "clinical consequence" because it removed the need to prescribe additional lipid-altering therapy or increase the dose of existing LDL-C lowering therapy. *See* Ex. 19, '728 Patent File History, Bays Declaration IV ¶ 41 (AMRN00212357) ("If LDL-C does not rise, as was the case with [ethyl-EPA] in the MARINE trial, then such a therapeutic intervention may not require additional lipid-altering drug therapy (such as the use of a statin), or an increase in the dose of existing LDL-C lowering therapy. This ***differential effect is of clinical consequence for both clinicians and patients***." (emphasis added).)

The applicants emphasized the important "clinical implications" of the extreme 49% increase in LDL-C levels in patients being treated with Lovaza®, as well as smaller increases of about 6%. (Ex. 19, '728 Patent File History, 6/27/12 Applicant Response at 25 (AMRN00212327); *see also* Ex. 18, '727 Patent File History, Weintraub Declaration II ¶ 23

(ARMN03059086).) The rise in LDL-C observed with Lovaza® required its prescribing information carry the warning that patients "'***should be monitored to ensure that the LDL-C level does not increase excessively.'"*** (Ex. 18, '727 Patent File History, Weintraub Declaration II ¶ 23 (AMRN03059086) (*citing* the Lovaza® package insert at page 8, Table 2).) But even smaller increases in LDL-C have clinical significance. Dr. Weintraub explained that "[e]ven a small increase in LDL caused by a triglyceride lowering drug can have serious complications for the patient. For example, an increase in concentration of LDL by about 6% can result in a need to double the concentration of a statin (if the patient can tolerate a statin) to mitigate this increase in LDL levels." (Ex. 18, '727 Patent File History, Weintraub Declaration II ¶ 23; *see also* Ex. 19, '728 Patent File History, 6/27/2012 Applicant Response at 25 (AMRN00212327); *see also* Ex. 18, '727 Patent File History, 9/21/11 Request for Continued Examination at 13 (AMRN03059047) (reporting that an increased LDL-C of 4.5% "requires clinical judgment.").) Indeed, Dr. Miller agrees that an increase in LDL-C levels of about 6% is clinically meaningful and can cause a clinician to consider modifying a patient's treatment regimen. (Miller Decl. ¶¶ 85–86.)

Based on these statements during prosecution, a skilled artisan would have understood that the terms "without substantially increasing LDL-C," "substantially no increase or a reduction in fasting LDL-C," and "substantially no increase in LDL-C" to mean "without a clinically meaningful increase in LDL-C." In other words, a skilled artisan would understand these terms to refer to the absence of an increase in LDL-C which could require modification of a patient's treatment; such as the increases seen with other TG-lowering therapies such as Lovaza® and fibrates. (Miller Decl. ¶ 81.)

2. "Without Substantially Increasing LDL-C," "Substantially No Increase Or A Reduction In Fasting LDL-C," and "Substantially No Increase In LDL-C" Are Not Indefinite

Defendants have offered no construction for these terms, alleging only that they are indefinite. Patent claims are presumed valid and thus are presumed to meet the requirements of § 112. 35 U.S.C. § 282. Defendants can only overcome the presumption of definiteness with clear and convincing evidence. *Sonix Tech.*, 844 F.3d at 1377. Defendants cannot meet this high bar.

35 U.S.C. § 112 requires that "a patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus*, 134 S. Ct. at 2129. Thus, while the Defendants assert that specific terms within the claim are indefinite, the proper inquiry in an indefiniteness analysis is whether the claim as a whole fails to inform skilled artisans about the scope of the invention with reasonable certainty.

The § 112 indefiniteness requirement is "part of the delicate balance the law attempts to maintain between inventors, who rely on the promise of the law to bring the invention forth, and the public, which should be encouraged to pursue innovations, creations, and new ideas beyond the inventor's exclusive rights." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki*, 535 U.S. 722, 731 (2002). The Supreme Court recognized that "the definiteness requirement must take into account the inherent limitations of language," but also require claims "be precise enough to afford clear notice of what is claimed." *Nautilus*, 134 S. Ct. at 2128–29. The Supreme Court's test for indefiniteness "mandates clarity, while recognizing that absolute precision is unattainable." *Id.* at 2129.

The use of the term "substantially" in "without substantially increasing LDL-C," "substantially no increase or a reduction in fasting LDL-C," and "substantially no increase in

LDL-C" do not render the claims indefinite. The Federal Circuit has "repeatedly confirmed that relative terms such as 'substantially' do not render patent claims so unclear as to prevent a person of skill in the art from ascertaining the scope of the claim." *Deere & Co.*, 703 F.3d at 1359. "The question is not whether the word 'substantially' has a fixed meaning as applied to [the claim term,] but how the [claim term] would be understood by persons experienced in this field . . . upon reading the patent documents." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1119–20 (Fed. Cir. 2002); *see also One-E-Way, Inc. v. ITC*, 859 F.3d 1059, 1067 (Fed. Cir. 2017) ("While we note that 'virtually' is a term of degree, one that slightly expands the scope of the term 'free from interference,' the inclusion of 'virtually' in these claims does not render them indefinite."). Here, the term "substantially" expands the scope of the disputed terms in a way that is understood by a skilled artisan, and does not render the claims so unclear as to support a finding of indefiniteness.

The fact that the "substantially" terms served to distinguish the claims from the prior art also confirms that a POSA would understand the terms' scope. In *Verve*, the Federal Circuit emphasized that "[i]t is well established that when the term 'substantially' serves reasonably to describe the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish the claimed subject matter from the prior art, it is not indefinite." 311 F.3d at 1120. Here, the applicants used the "substantially" terms to distinguish the claimed subject matter from the prior art. During prosecution, there was extensive discussion regarding the importance of ethyl-EPA's ability to lower TG levels without substantially increasing LDL-C. As discussed above, the applicants submitted a number of declarations during prosecution to explain how, prior to the claimed invention, medications used to lower TG levels often "increase[d] LDL-C levels, and sometimes ***substantially*** so especially in patients with very high

TG levels." (Ex. 19, '728 Patent File History, Bays Declaration IV ¶ 40 (AMRN00212357) (emphasis added); *see also* Ex. 18, '727 Patent File History, Weintraub Declaration I ¶ 16 (AMRN03058277) ("[The claimed invention], therefore has the potential to fill a clinically important unmet medical need as a result of the ***substantial LDL-C increasing*** effect of currently approved omega-3 and fibrate drugs." (emphasis added).)

Moreover, the Examiner explicitly stated in the Notice of Allowance that the long-felt need for a treatment for patients with severely elevated TG that "not only reduces the level of TG but also does not increase LDL-C which is associated . . . with an increase in cardiovascular diseases," justified the "allowance of the instant claims in their full scope." (Ex. 19, '728 Patent File History, 9/6/12 Notice of Allowance at 3–6 (AMRN00212745–48).) The Notice of Allowance demonstrates the Examiner's understanding that ethyl-EPA was different from prior TG-lowering therapies in that it did not cause a substantial increase in LDL-C levels. Defendants' improper attempt to invalidate claims by arguing that the terms describing the critical inventive aspect of the claims are indefinite should be denied.

If the court agrees that these terms are not indefinite, Plaintiffs' proposed constructions should be adopted for the additional reason that Defendants have failed to offer any alternative construction. *See, e.g., Constant Compliance, Inc. v. Emerson Process Mgmt. Power & Water Solutions, Inc.*, 598 F. Supp. 2d 842, 848 (N.D. Ill. 2009) (finding defendant waived right to make claim construction argument, and adopting plaintiffs' construction); *see also Bristol-Myers Squibb Co. v. Apotex, Inc.*, No. 10-5810, 2013 WL 1314733, *26–27 (D.N.J. Mar. 28, 2013) (adopting plaintiffs' plain meaning where defendant solely argued indefiniteness).

G. "without increasing LDL-C" and "without an increase . . ." [22]

Amarin's Proposal	Defendants' Proposal
No Construction Necessary / Plain and Ordinary meaning	Indefinite under 35 U.S.C. § 112

The terms "without increasing" and "without an increase" are common and should be given their plain and ordinary meaning. "[T]he words of a claim 'are generally given their ordinary and customary meaning' . . . that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips*, 415 F.3d at 1312–13. A skilled artisan would have readily understood the ordinary and customary meaning of "without increasing LDL-C" and "without an increase . . ." such that a construction is not necessary.

Many of the asserted claims with these terms specify that LDL-C would not be increased by more than a specific amount. For example, Claim 4 of the '560 Patent recites "without increasing LDL-C by more than 5% in the subject." The meaning of these terms is clear—the increase is no more than 5%. (Miller Decl. ¶¶ 90, 92.)

Even when a numerical amount is not identified, for example "without increasing LDL-C in the subject" ('560 Patent at Claim 7), a person of ordinary skill in the art would have understood the scope of these claims to refer to an effect without *any* increase in LDL-C levels in the subject. There is no ambiguity in these claims as well—any increase in LDL-C value would be outside the scope of these claims. (*See also* Miller Decl. ¶¶ 90, 91.)

Similar to the previous terms, Defendants have offered no construction, contending only that the terms are indefinite. Patent claims are presumed valid and thus are presumed to meet the

[22] The claims containing these terms are: '560 Patent, claims 4, 7, 14, 17; '650 Patent, claims 4, 7, 11, 14; '929 Patent, claim 4; '372 Patent, claims 4, 13, 20; '594 Patent, claims 1, 4, 10, 13, 17, 20.

requirements of definiteness. 35 U.S.C. § 282. Defendants cannot meet the high burden of demonstrating indefiniteness by clear and convincing evidence. *Sonix Tech.*, 844 F.3d at 1377.

H. "without effecting a statistically significant increase in LDL-C" [23]

Amarin's Proposal	Defendants' Proposal
without bringing about a rise in LDL-C attributable to the treatment rather than to chance	Indefinite under 35 U.S.C. § 112

Plaintiffs' proposed construction accords the term "without effecting a statistically significant increase in LDL-C" its plain meaning, *i.e.*, "without bringing about a rise in LDL-C attributable to the treatment rather than to chance."

Amarin's proposed construction of the term is consistent with the prosecution history. In describing the clinical trial for the claimed invention, the applicants state that a "statistically significant increase in LDL-C was expected." (Ex. 19, '728 Patent File History, 6/27/12 Applicant Response at 18 (AMRN00212320); *see also* Ex. 18, '727 Patent File History, Bays Declaration I ¶ 11 (AMRN03058235).) But contrary to this expectation, the clinical trial results demonstrated that purified ethyl-EPA "significantly reduced triglyceride[] levels at both the 2g/day and 4g/day doses without any ***statistically significant*** change in LDL-C." (Ex. 18, '727 Patent File History, Bays Declaration I ¶ 13 (AMRN03058235) (emphasis added); *see also* Miller Decl. ¶ 95.) These statements demonstrate the understanding that a "statistically significant increase" was one that was attributed to treatment with purified ethyl-EPA rather than chance.

Dr. Miller explains that statistical significance is a well understood term in clinical research. (Miller Decl. ¶ 94.) Statistical significance is reached only when the clinical trial

[23] The claims containing these terms are: '715 Patent, claims 13, 14.

results demonstrate that an observed difference between the treatment group and placebo group is attributable to treatment rather than to chance. (Miller Decl. ¶ 94.) A person of ordinary skill in the art reading the claims would have understood the scope of the term "without effecting a statistically significant increase in LDL-C" to mean that a clinician would administer the treatment with the intent to reduce TGs "without bringing about a rise in LDL-C attributable to the treatment rather than to chance." (Miller Decl. § VII.G.)

Again, Defendants cannot reach the high bar of demonstrating indefiniteness by clear and convincing evidence. *Sonix Tech.*, 844 F.3d at 1377.

I. "compared to placebo control" and "placebo control"[24]

Claim Term	Amarin's Proposal	Defendants' Proposal
"compared to placebo control"	compared to not administering treatment	compared to a subject who is administered a placebo and not concurrently administered a pharmaceutical composition comprising ethyl eicosapentaenoate
"placebo control"	not administering treatment	a subject who is administered a placebo and not concurrently administered a pharmaceutical composition comprising ethyl eicosapentaenoate

As discussed in Section E above, a person of ordinary skill in the art would have readily understood the plain and ordinary meaning of the "compared [to]" terms within the context of each claim, such that a construction is not necessary. In addition, "placebo control" is a well understood term in clinical research. (Miller Decl. ¶ 98.) As Dr. Miller explains, a skilled artisan would understand the term "placebo control" in the claims to be the counterpart to the

[24] The claims containing these terms are: '560 Patent, claims 11, 14–17; '650 Patent claims 8, 11–14; '677 Patent, claims 1, 6–9, '446 Patent, claims 1, 4–7.

individual being treated, *i.e.*, an individual who is not administered treatment. (Miller Decl. ¶ 98.) Plaintiffs' proposed construction properly reflects the plain meaning of the term "placebo control" as "not administering treatment."

By proposing that "placebo control" be construed as "a subject who is administered a placebo and not concurrently administered a pharmaceutical composition comprising ethyl eicosapentaenoate," Defendants appear to be attempting to add a requirement that a clinician also administer a placebo. This attempt is misplaced and conflicts with how a person of ordinary skill would understand the claims in the context of the patent and prosecution history.

A skilled artisan would have understood the claims to be referring to a comparison between the subject undergoing treatment and a subject who is not administered treatment. (Miller Decl. ¶ 98.) Indeed, this understanding is consistent with evidence-based medicine, in which clinicians rely on clinical trials to provide information concerning the effects of the drugs that they use to treat patients. (Miller Decl. ¶ 98.) Thus, a person of ordinary skill in the art would understand "compared to placebo control" to mean "compared to not administering treatment."

J. "identifying a group of subjects"[25]

Amarin's Proposal	Defendants' Proposal
identifying a class of individuals	identifying a group of two or more subjects

The claim term "identifying a group of subjects" is found in the '372 and '594 Patents. For example, the '372 Patent at Claim 1 states:

> A method of reducing triglycerides comprising, ***identifying a group of subjects*** having a median triglyceride level of at least 500

[25] The claims containing these terms are: '372 Patent, claims 1, 10, 17; '594 Patent, claims 1, 10, 17.

> mg/dl and orally administering daily to at least one subject in the ***group of subjects*** a pharmaceutical composition comprising about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids, for a period of 12 weeks to reduce fasting triglycerides in the at least one subject.

The "one subject" who is administered treatment belongs to the "group of subjects" who have "a median triglyceride level of at least 500 mg/dl." Thus, these claims are directed to a subject who belongs to a specific group of individuals with a median TG level of at least 500 mg/dl. As explained by Dr. Miller, hypertriglyceridemic patients are divided into three different classes depending on the level of TGs in the blood: borderline high (150–199 mg/dl), high (200–499 mg/dl), and severe (≥ 500 mg/dl). (Miller Decl. ¶ 33.) Patients are divided into these classes because each class is considered distinct with respect to treatment goals and approaches to treatment. (Miller Decl. ¶ 34.) Therefore, a skilled artisan would understand "identifying a group of subjects having a median triglyceride level of at least 500 mg/dl," to be referring to the recognized class of hypertriglyceridemic patients with TG levels of at least 500 mg/dl. (Miller Decl. ¶¶ 101–102.) Clinicians recognize that a patient belongs to a particular class, for example the class with severely elevated TG. This is what the patent example describes.

Indeed, throughout prosecution, the applicants emphasized the unique nature of the claimed patient population, subjects with TG levels above 500 mg/dl. In a declaration submitted to the PTO, Dr. Bays explained that "guidelines and clinical trial data support[] that patients with borderline high/high triglyceride levels (150 mg/dl – 499 mg/dl) substantially differ from patients with very high triglyceride levels (≥ 500 mg/dl). This difference is reflected in established diagnostic and treatment guidelines, regulatory considerations, and responses to therapeutic interventions." (Ex. 19, '728 Patent File History, Bays Declaration IV ¶ 15 (AMRN00212352); *see also* Ex. 32, '594 Patent File History, Weintraub Declaration II ¶ 8

(AMRN00289355) ("patients with borderline high/high triglycerides . . . can respond very differently to triglyceride lowering therapy than do subjects with very high triglycerides" (citing ATP III).)

In addition, in the Notice of Allowance for the '728 Patent, the Examiner recognized that the "prior art does not teach administration of ethyl-EPA to patients having TG levels between 500 and 1500 mg/dl (very high)" (Ex. 19, '728 Patent File History, 9/6/12 Notice of Allowance at 3 (AMRN00212745)), distinguishing the claimed severely elevated TG patient population from patients with borderline-high or high TG levels (150 mg/dl – 499 mg/dl). (*See also* Ex. 32, '594 Patent File History, 9/17/13 Notice of Allowance at 2 (AMRN00289715) ("Applicants demonstrated that the patient populations disclosed by Katayama et al. [], Hayashi et al. [] and Grimsgaard et al. [] are different from the patient population recited in instant claims.").) Given the repeated emphasis on the severely elevated TG group as a class throughout the prosecution history, a person of ordinary skill in the art would have understood the term "identifying a group of subjects" to refer to "identifying a class of individuals," not merely "identifying a group of two or more subjects" as Defendants propose.

K. "patient population" [26]

Amarin's Proposal	Defendants' Proposal
a class of subjects	group of two or more patients

The claims recite that the claimed "patient population" has a fasting baseline TG level of "at least 500 mg/dl" or "about 500 mg/dl to about 1500 mg/dl." For example, Claim 10 of the '652 Patent states:

> A method of lowering triglycerides in a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters, which when orally administered in a first ***patient population*** having said baseline triglyceride level and receiving, for a period of twelve weeks, 4 g per day of the pharmaceutical composition, is effective to reduce said baseline triglyceride level without substantially increasing LDL-C compared to a second ***patient population*** having said baseline triglyceride level that has not received the pharmaceutical composition.

Therefore, the term "patient population" is directed to subjects with fasting baseline TG levels greater than or equal to 500 mg/dl. As explained in Section J, hypertriglyceridemic patients are divided into three different classes depending on the level of TGs in the blood, and each class is considered distinct with respect to treatment goals and approaches to treatment. (Miller Decl. ¶¶ 33–34.) Therefore, a person of ordinary skill in the art would have understood "patient population" to refer to the recognized class of hypertriglyceridemic patients with TG levels of at least 500 mg/dl. (Miller Decl. § VII.J.)

[26] The claims containing these terms are: '698 Patent, claims 1, 4, 5; '652 Patent, claims 10, 15–18; '728 Patent, claim 19.

Plaintiffs' construction is also supported by the prosecution history. As discussed above, the applicants emphasized the unique nature of the claimed patient population, subjects with TG levels above 500 mg/dl. (*See, e.g.*, Ex. 19, '728 Patent File History, Bays Declaration IV ¶ 15 (AMRN00212352) ("guidelines and clinical trial data support[] that patients with borderline high/high triglyceride levels (150 mg/dl – 499 mg/dl) substantially differ from patients with very high triglyceride levels ($\geq$ 500 mg/dl).").) In addition, in the Notice of Allowance for the '728 Patent, the Examiner distinguished the claimed severely elevated TG patient population from patients with borderline-high or high TG levels (150 mg/dl – 499 mg/dl). (*See, e.g.*, Ex. 19, '728 Patent File History, 9/6/12 Notice of Allowance at 3 (AMRN00212745).) Given the repeated emphasis on the severely elevated TG group as a class throughout the prosecution history, a person of ordinary skill in the art would have understood the term "patient population" to refer to "a class of subjects," not "a group of two or more patients" as Defendants propose.

VI. CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request that the Court adopt their proposed claim constructions.

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Respectfully submitted,

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